

**REMARKS**

The Examiner rejects claims 1-7 and 9-16 in the subject application. Applicants amend claims 1 and 16. Claims 1-7 and 9-16 (2 independent claims; 15 total claims) remain pending in the application.

Support for the various amendments may be found in the originally filed specification, claims, and figures. No new matter has been introduced by these amendments. Reconsideration of this application is respectfully requested.

**IN THE CLAIMS**

Claim 1 is amended to rewrite steps (a) to (c) as method steps, as suggested by the Examiner.

Claim 16 is amended to correct the typographical error, wherein "family" replaces the misspelled "familey."

Claims 1 and 16 are further amended to clarify that "R" as set forth in Formula II is a terminal group.

**IN THE SPECIFICATION**

The specification is amended to clarify that "R," as presented in Formula II throughout the application, is a terminal group.

**35 U.S.C. §112 REJECTION**

Claims 1-7 and 9-16 stand rejected under 35 U.S.C. §112, as purportedly being indefinite. In particular, the Examiner alleges that in Formula II of Claims 1 and 16, "R" is bonded to either sides, i.e., not depicted as a terminal group, but to form a covalent bond with a protein, the functional group "R" needs to be a terminal group. Therefore, according to the Examiner, it is not clear how "R" not being a terminal group, can react with a protein to form a covalent linkage. Applicants have amended Formula II in Claims 1 and 16 to reflect that "R" is a terminal group. Accordingly, Applicants request withdrawal of this rejection.

Applicant's have also amended Formula II throughout the specification, as noted above, to reflect that "R" is a terminal group. Proper support for the amendment to the

claims in the specification is satisfied since it is obvious to one skilled in the art that "R" of Formula II is a terminal group. No new matter has been added by these amendments.

Claims 1-7 and 9-15 stand rejected as being indefinite and confusing. In particular, the Examiner states that steps "(a)"- "(c)" of Claim 1 should be rewritten as method steps because as the Claim currently reads, it appears that "steps (a) to (c)" describe components of composition. Applicants have amended Claim 1 to clarify that steps "(a)" -"(c)" are method steps, thereby obviating the Examiner's rejection.

### **35 U.S.C. §103 REJECTIONS**

The Examiner again rejects claims 1-16 under 35 U.S.C. §103(a) as allegedly being unpatentable over each of: 1) Yuan et al., Anal. Chem. 1998, Vol. 70, No. 3, pp. 596-601 ("Yuan") or Matsumoto et al., U.S. Patent No. 5,859,297 ("Matsumoto") and in view of 2) Pennanen et al., Int. J. Immunopharmacol. 1995, Vol. 17, No. 6, pp. 475-480 ("Pennanen"). Applicants respectfully traverse the rejection.

To render a claim obvious, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. There must be a reasonable expectation of success. In addition, the prior art relied upon must teach or suggest all the claim limitations. None of these criteria are met in this case.

The Examiner asserts that Yuan discloses that BHHCT resulted in superior detection over conventional fluorescent labels and Matsumoto discloses use of streptoavidin and BHHCT in an immunoassay for alpha-fetoprotein. The Examiner further asserts that Pennanen discloses time resolved immunodetection of cytokines, and as such, motivation existed to combine these references and achieve the present invention. Applicants disagree.

As a preliminary matter, Applicants submit that one skilled in the art would not be motivated to combine the cited references of Yuan and Matsumoto with Pennanen to achieve the claim limitations of amended Claim 1. Yuan and Matsumoto are directed to the problem of detecting cytokines, and disclose the use of BHHCT when in assays to detect the tumor marker alpha-fetoprotein, present at high levels.

Pennanen is also directed to detecting cytokines, but in an *in vitro* cell system, not a biological sample. Furthermore, the detection system disclosed therein is based on a cell line that is activated to produce *increased* amounts of cytokines. One skilled in the art would expect such cytokines to be present at a higher concentration in such a system than in a biological sample, and thus easy to detect. Therefore, any disclosure relating to the detection of such cytokines would not motivate one skilled in the art to assume that such could also be applied to naturally occurring chemokines which, as discussed in Leonard<sup>1</sup>, have a low effective or free concentration in serum.

Moreover, the Examiner contends that Pennanen discloses detection of cytokine by time resolved immunoassay with the only difference being that they do not teach fluorescent structure portion (BHHCT). The Examiner further contends that while  $\beta$ -diketone fluorescent structure portion (BHHCT) is known in the art to greatly improve fluorescent detection in time resolved immunoassay, one skilled in the art would obviously be motivated to include cytokine of Pennanen as an equivalent analyte in the method of Yuan or Matsumoto utilizing BHHCT, with the expectation of detecting/measuring cytokine with a high sensitivity in the sample. Applicants disagree and submit that the Examiner is relying upon improper hindsight to combine the teachings of the prior art in an attempt to render the present invention obvious. Pennanen already discloses a method of detection; thus, there is no motivation to seek out the fluorescent structure portion (BHHCT) as an additional detector for a time resolved immunoassay.

Furthermore, the methods and kits of the amended claims make possible the detection of a chemokine in biological fluid samples. Such could not be achieved by conventional techniques available in the cited art as of the priority date. This is an unexpected and significant effect which is qualitatively different from the results obtained using conventional techniques.

Moreover, even if the references are combined (even though there is no teaching or motivation to do so) the combination does not teach the claimed invention. In particular, no combination of the references teaches or suggests detecting cytokines in a biological fluid sample by:

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<sup>1</sup> Edward J. Leonard, Plasma Chemokine and Chemokine-Autoantibody: Complexes in Health and disease (1998).

forming a composite by (a) binding a first antibody, including a portion bound to a solid phase and a region bindable to a cytokine, to a solid phase; (b) adding the sample containing the cytokine; (c) binding a second antibody, including a region bindable to the cytokine and a portion to which biotin is bound, to the cytokine; (d) a conjugate including streptoavidin or avidin and a fluorescent structural portion capable of being complexed with a lanthanoid metal ion; and (e) the lanthanoid metal ion are bound, the composite being formed on the solid phase; and

measuring fluorescence of the fluorescent structural portion which has been complexed with the lanthanoid metal ion,

wherein the method comprises a step of washing after each of steps (a) to (c); and

wherein the cytokine is a cytokine belonging to the chemokine family, and

wherein the fluorescent structural portion is represented by General Formula (I):



(where R is a residue which is a functional group capable of forming a covalent bond with a protein; Ar is a hydrocarbon group having a conjugated double bond system; n is an integer equal to or greater than 1; and X is a fluorine atom or a group represented by General Formula (II):

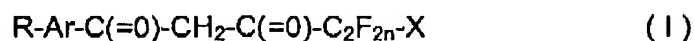


as set forth in Claim 1 or a kit including:

a first antibody including a portion bound to a solid phase and a region bindable to a cytokine; a second antibody including a region bindable to the cytokine and a portion to which biotin is bound; a conjugate including streptoavidin or avidin and a fluorescent structural portion capable of being complexed with a lanthanoid metal ion; and the lanthanoid metal ion,

wherein the cytokine is a cytokine belonging to the chemokine family, and

wherein the fluorescent structural portion is represented by General Formula (I):



(where R is a residue which is a functional group capable of forming a covalent bond with a protein; Ar is a hydrocarbon group having a conjugated double bond system; n is an integer equal to or greater than 1; and X is a fluorine atom or a group represented by General Formula (II):



as set forth in Claim 16.

The Examiner states that Applicants have not provided reasoning as to why chemokines would not be expected to be equivalent analytes. The Examiner should note that chemokines are present in serum at dramatically lower levels than other cytokines, as evidenced by Leonard. One skilled in the art would not assume that such low levels could be measured by similar methods.

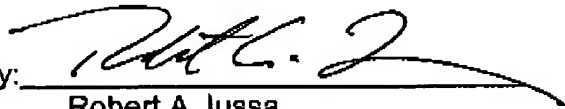
Accordingly, Yuan, Matsumoto, and Pennanen fail to combine or modify the teachings of the prior art to produce the claimed invention, and there is no teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art.

**CONCLUSION**

Applicants respectfully submit that the present application is now in condition for allowance. Reconsideration of the application is thus requested. Applicants invite the Examiner to telephone the undersigned if he or she has any questions whatsoever regarding this Response or the present application in general.

Respectfully submitted,

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